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Synthesis of Tetrahydrofurans by a Tandem Hydrogen Atom Abstraction/ Radical Nucleophilic Displacement Sequence

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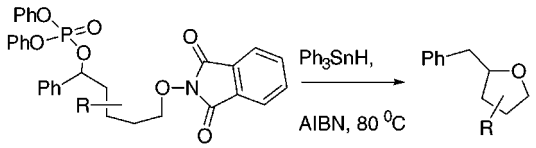
ABSTRACT



The reaction of a series of 5-(*N*-phthalimidoxy)-1-phenyl-1-(diphenylphosphatoxy)pentanes with triphenyltin hydride and AIBN provides alkoxy radicals which undergo 1,5-hydrogen atom abstraction to give *β*-(phosphatoxy)alkyl radicals. These radicals then take part in a radical nucleophilic displacement leading, after chain transfer, to tetrahydrofurans.

Well-planned tandem radical sequences, enabling the construction of complex molecular architectures from relatively simple precursors, are some of the most powerful transforms in modern organic chemistry.[2] Radical polar crossover sequences, in which a radical reaction is coupled to an oxidation or reduction followed by a two-electron process, represent a possible means of further augmenting the power of tandem schemes. For example, in the reductive sphere, samarium diiodide allows radical processes to be coupled to subsequent nucleophilic processes, via the trapping of radicals as organosamarium III species.[3−5] On the other hand, the potential of radical cyclizations followed by oxidation to cations and eventual trapping has been elegantly demonstrated by Murphy using the combination of arenediazonium salts and tetrathiafulvalene.[6,7]

We recently described a novel radical process,[8] predicted computationally by Zipse,[9,10] in which an alcohol displaced a phosphate group from a *β*-(phosphatoxy)alkyl radical (**1**) to give the vicinally substituted radical (**2**) (Scheme 1). Preliminary kinetic[8] and stereochemical[11] data were consistent with either a concerted displacement on the initial radical or trapping of a contact ion pair arising from heterolysis of the *β*-(phosphatoxy)alkyl radical. We set out below our first attempts to develop this type of vicinal radical nucleophilic substitution into a synthetically useful tandem type sequence.

The synthesis of tetrahydrofurans presented focuses on the cyclization onto the *β*-(phosphatoxy)alkyl radical with vicinal displacement of the phosphate group. The initial challenge

(1) University of Illinois at Chicago; (b) Wayne State University.
(2) For a collection of reviews dealing with all aspects of tandem reactions, see: *Chem. Rev.* **1996**, *96*, issue 1 (Wender, P. A., Ed.).
(3) Curran, D. P.; Fevig, T. L.; Jasperse, C. P.; Totleben, M. J. *Synlett* **1992**, 943.
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(9) Zipse, H. *Angew. Chem., Int. Ed.* **1994**, *33*, 1985.
(10) Zipse, H. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2691.
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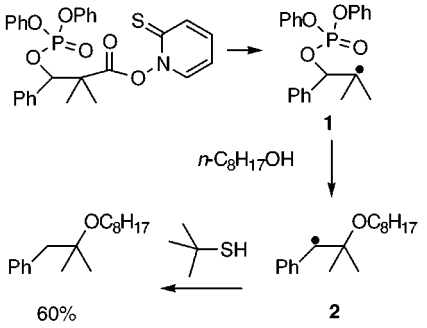
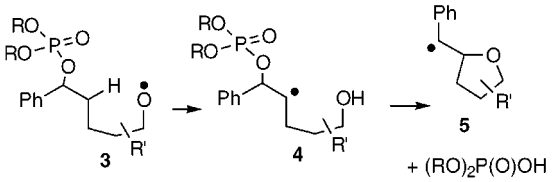
Scheme 1. Radical Nucleophilic Displacement



was one of designing suitable precursors for the β-(phosphatoxy)alkyl radical that are compatible with an intramolecular nucleophile. Thus, it was felt that PTOC esters, as used in the initial kinetic work, or bromides, as employed in the stereochemical analysis, would not be suitable owing to the potential for nucleophilic cyclizations prior to radical cyclization. Phenylthio or phenylselenyl groups were found to be unsuitable precursors owing either to a lack of reactivity toward tin hydrides or to instability with respect to thiiranium or seleniranium ion formation. In light of these potential complications, we elected to take advantage of the built-in alcohol and to use it, in the form of an alkoxyl radical, to generate the β-(phosphatoxy)alkyl radical by 1,5-hydrogen atom abstraction. This approach to the problem, aside from giving rise to a tandem radical/polar sequence (Scheme 2),

Scheme 2. Tandem Hydrogen Abstraction/Cyclization Sequence

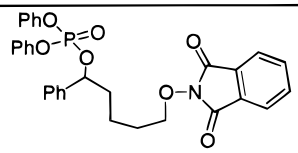
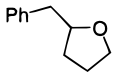
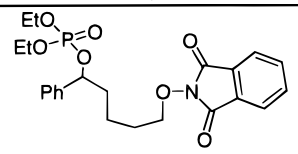
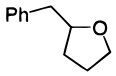
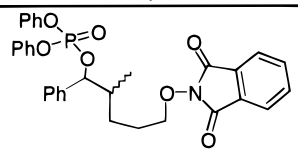
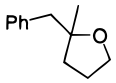
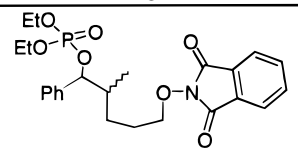
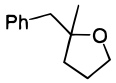
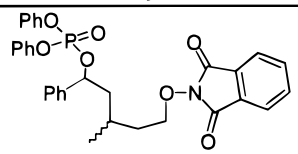
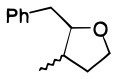
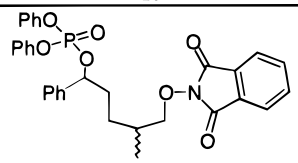
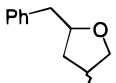


has the considerable advantage of simplifying the substrate and its preparation. One obvious pitfall, which could only reliably be addressed experimentally, was the potential for a competing 1,6-hydrogen abstraction from the benzylic position.

The tin hydride-mediated cleavage of *N*-alkoxyphthalimides[12] was selected as an appropriate means of alkoxy radical generation, and this functionality was readily incorporated into a number of phosphate esters (**6**−**11**) by straightforward procedures as outlined in the Supporting Information.

Treatment of a solution of **6** in benzene at reflux dropwise with Ph_3SnH and AIBN resulted in a crude reaction mixture containing a single resonance in its ^{31}P NMR spectrum (δ −23.1), which was assigned to a salt of diphenylphosphoric acid. The ^1H NMR spectrum of the reaction mixture revealed the exclusive formation of 2-benzyltetrahydrofuran (**12**), which was subsequently isolated in 95% yield (Table 1).

Table 1. Formation of Tetrahydrofurans[17]

SUBSTRATE	PRODUCTS (% YIELD)
 **6**	 **12** (95)
 **7**	 **12** (60) + **16** (25) + **17** (15)
 **8**	 **13** (90)
 **9**	 **13** (85)
 **10**	 **14** (90) ~ 1/1 mixture
 **11**	 **15** (92) ~ 55/45 mixture

When the same reaction conditions were applied to the analogous diethyl phosphate **7**, the outcome was less clear-cut. The ^1H NMR spectrum indicated the formation of **12** and two other substances, which were subsequently assigned as the product of β-(phosphatoxy)alkyl migration[13−16] (**16**) (Figure 1) and the reduction product (**17**), in the ratio 60/25/15 (Table 1). The ^{31}P NMR spectrum, with three signals, was consistent with this interpretation. Evidently, the nature

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(13) Crich, D.; Yao, Q. *J. Am. Chem. Soc.* **1993**, *115*, 1165.
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(15) Choi, S.-Y.; Crich, D.; Horner, J. H.; Huang, X.; Newcomb, M.; Whitted, P. O. *Tetrahedron* **1999**, *59*, 3317.
(16) Beckwith, A. L. J.; Crich, D.; Duggan, P. J.; Yao, Q. *Chem. Rev.* **1997**, *97*, 3273.

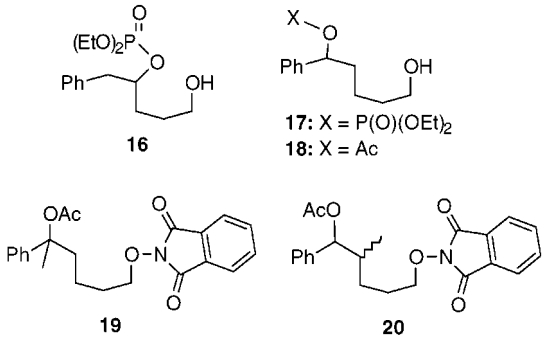


Figure 1.

of the leaving groups has a significant effect on the outcome of the reaction.

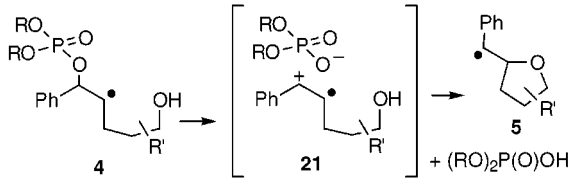
Application of the same conditions to the substrates **8** and **9**, containing a methyl group at the site of hydrogen atom abstraction, resulted in both instances in the formation of the tetrahydrofuran **13** in excellent yield (Table 1). ^{31}P NMR spectroscopy of the crude reaction mixtures indicated only one significant phosphorus-containing product in each case, namely, the expelled phosphate. Thus, the inclusion of a methyl group at the site of abstraction and substitution facilitates displacement of the weaker leaving group diethyl phosphate.

Moving the methyl substituent one and two carbons along the aliphatic chain, as in **10** and **11**, led to the isolation of the tetrahydrofurans **14** and **15** in excellent yields (Table 1). Unfortunately, there was no diastereoselectivity in either of these two cyclizations under the conditions that were employed. The remote possibility exists that the individual diastereomers of both **10** and **11** cyclize with excellent but opposite selectivity, resulting in the observed mixtures. However, we consider this to be extremely unlikely in light of the very poor selectivity noted in the intermolecular displacements previously studied.[11]

We also prepared the three acetates **18**−**20** but found no evidence for tetrahydrofuran formation in any of their reactions with Ph_3SnH. These results are consistent with the notion that acetate is an even weaker nucleofuge than diethyl phosphate.

Two major points emerge from the above results. First, 1,6-hydrogen atom abstraction from the benzylic position did not compete effectively with 1,5-hydrogen atom abstraction leading to the requisite β-(phosphatoxy)alkyl radicals. Self-evidently, the benzylic C−H bond is the weaker one, and we are therefore led to attribute this regioselectivity to a polar effect in which the strongly withdrawing phosphate groups destabilize the transition state for benzylic hydrogen abstraction by the electrophilic alkoxyl radical. Obviously, the usual entropic factors also favor the 1,5-abstraction observed. Second, the substituent effects, particularly the contrast between **7** and **9**, and lack of stereoselectivity (**10** and **11**) strongly suggest that the reaction is proceeding via a stepwise fragmentation of the β-(phosphatoxy)alkyl radical to give a styrene radical cation/phosphate anion pair (**21**) followed by ring closure to give the more stable benzylic radical (Scheme 3). Indeed, recent work on the mechanism of the β-(phosphatoxy)alkyl rearrangement is strongly supportive of a dissociative mechanism.[18]

Scheme 3. Proposed Dissociative Mechanism



All of the above examples result in the formation of benzylically stabilized radicals. However we anticipate, from consideration of the relative ease of β-(phosphatoxy)alkyl rearrangements,[14] that simple tertiary alkyl radical formation would be sufficient.

Further studies on the mechanisms of these intriguing reactions as well as on their applications in synthesis are currently underway and will be described in due course.

Acknowledgment. We thank the NSF (Grants CHE 9625256 and CHE 9614968) for support to D.C. and M.N., respectively, and the University of Illinois at Chicago for a University Fellowship (X.H.).

Supporting Information Available: Description of the preparation of all substrates and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL990564B

(17) New compounds had spectral and microanalytical or HRMS data consistent with the assigned structures.

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